

# **Interactive effects of antioxidant genes and air pollution on respiratory symptoms: a HuGE systematic review**

*Protocol for a HuGE review on gene-environment interactions*

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*Potential conflict of interest*

None.

## Background

Air pollution is known to affect the lung, especially in people with asthma and Chronic Obstructive Pulmonary Disease (COPD). Its daily variations have been associated with higher number of emergency visits and hospital admissions due to respiratory complaints, and higher respiratory mortality (Curtis 2006). In terms of risk magnitude, the respiratory effects of air pollution are relatively small in the population compared with other environmental exposures, but susceptibility to such effects varies widely between individuals, partly due to genetic factors.

Evidence suggests that oxidative stress in the lung is a unifying feature underlying the toxic actions of air pollutants (Kelly 2003), and therefore genes regulating the individual's antioxidant defences represent good candidates for possible interactions with air pollution (London 2007). Indeed, a number of genetic association studies, as well as experimental chamber studies with collection of genetic data, have suggested that individuals carrying variants of antioxidant genes (such as *GST* and *SOD* genes, *NQO1*, *EPHX*, *HMOX-1* and *CAT* among others) may be more susceptible to the respiratory effects of air pollution. However, the evidence which has been accumulating is somewhat difficult to interpret, given that different studies have evaluated different subgroups of people and different pollutants and genes. Moreover, detection of interaction effects requires sample sizes which can be four times larger than those needed to detect main effects (Smith 1984, Brookes 2004), and many of the current studies are underpowered to detect interactions between genes and air pollution.

Understanding genetic susceptibility to the effects of air pollution has important public health implications, and might lead to more effective preventive strategies targeted at individuals at risk, such as supplementation of dietary antioxidants. The aim of this systematic review is to provide an overall picture of the nature and magnitude of the interaction between genes and air pollution on respiratory symptoms and understand reasons for heterogeneity of study results. By using meta-analysis to pool results across similar studies, we also aim to overcome the problem of limited statistical power and provide more precise estimates of the gene-pollutant interaction effects.

## Methods

### **Criteria for study inclusion**

#### *Polymorphisms*

Polymorphisms of any gene known to influence the individual's antioxidant capacity. These include but are not limited to: *GSTP1*, *GSTT1*, *GSTM1*, *GSTM3*, *NQO1*, *NAT1*, *NAT2*, *CYP1A1*, *CYP1A2*, *SULT1A1*, *SULT1A2*, *SOD2* (also called *Mn-SOD*), *SOD3* (also called *EC-SOD*), *Ah receptor*, *Nrf2*, *EPHX1*, *HMOX-1* and *CAT*.

#### *Pollutants*

Any outdoor air pollutant, including particulate matter, ozone, nitrogen oxides and carbon monoxide.

### *Clinical outcomes*

Lung function and respiratory symptoms, in both healthy subjects and patients with airway disease, and risk of asthma. Other clinical outcomes, including hospital admissions or visits for respiratory complaints, will also be considered.

### *Types of studies*

*In vivo* studies of any study design in humans, assessing the interactive effects of antioxidant genes with air pollution on respiratory symptoms.

### **Search methods**

- Electronic search of: MEDLINE, EMBASE and ISI Web of Science
- Non-English language papers considered
- Cross-checking of reference lists of relevant papers (primary studies and reviews)
- Contact will be sought with authors of primary studies deemed to be eligible for inclusion but for which complete data were not available directly from publication

### **Data extraction**

Two reviewers will independently extract the data, with a third reviewer available for arbitration.

### **Quality assessment**

Criteria for the evaluation of study quality will be investigated and shall include traditional observational epidemiology factors such as study design, participant ascertainment, study size, and other potential biases. We will also evaluate the credibility of the cumulative evidence according to a semi-quantitative approach recently proposed by Ioannidis and colleagues (Ioannidis, 2007). No quality weights will be used in the meta-analysis models, but sensitivity analyses will be performed to assess the possible influence of quality on the pooled results.

### **Data synthesis**

The data will be pooled with random effects models, using per-genotype odds ratios. The presence of interaction between a gene polymorphism and a pollutant will be assessed by an interaction test, and the magnitude of the interaction will be evaluated as the probability of the effect of the pollutant on respiratory symptoms for mutant homozygotes and heterozygotes, compared with that of wild homozygotes. We will also investigate the use of a genetic model-free approach (Minelli 2005) extended to the evaluation of gene-environment interactions. Between-study heterogeneity will be investigated using the  $Q$  test and the  $I^2$  statistic, and the presence of publication bias will be assessed graphically, through funnel plots, and formally, using Begg's and Egger's tests. For each study, deviations from Hardy-Weinberg equilibrium (HWE) will be tested using the exact test, and the magnitude of the departure measured using the inbreeding coefficient. Studies with statistically significant and/or large deviations from HWE will be further investigated for methodological problems, including

population stratification and genotyping errors, but they will only be excluded from the analysis in the presence of evidence of such problems (Minelli *et al.*, 2008).

## References

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